

Exploring Novel Approaches to Shared TB Laboratory Services: California-Wisconsin Shared Services Pilot Study

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Outline

- Background and Objectives of the Shared Services Project
- Logistics of the Project
- Testing involved
- Results
- Conclusions

Background

- Although tuberculosis (TB) remains a significant burden to public and private health care organizations nationwide, the number of TB cases continues to decrease¹
- For laboratories in areas that are low-incidence for TB, it may be a struggle to offer a full spectrum of TB laboratory services in the face of ever-decreasing test volumes.
- Ongoing budgetary concerns and retirement of experienced laboratory professionals contribute to this struggle.

Background

- To maintain quality laboratory testing and to control expenses, laboratories may consider a variety of shared service options
 - Referral for specialized testing
 - Laboratory partnerships
- Laboratories are hesitant to explore these opportunities, as many aspects of shared laboratory services have not been fully examined.

Objectives of Shared Services Pilot

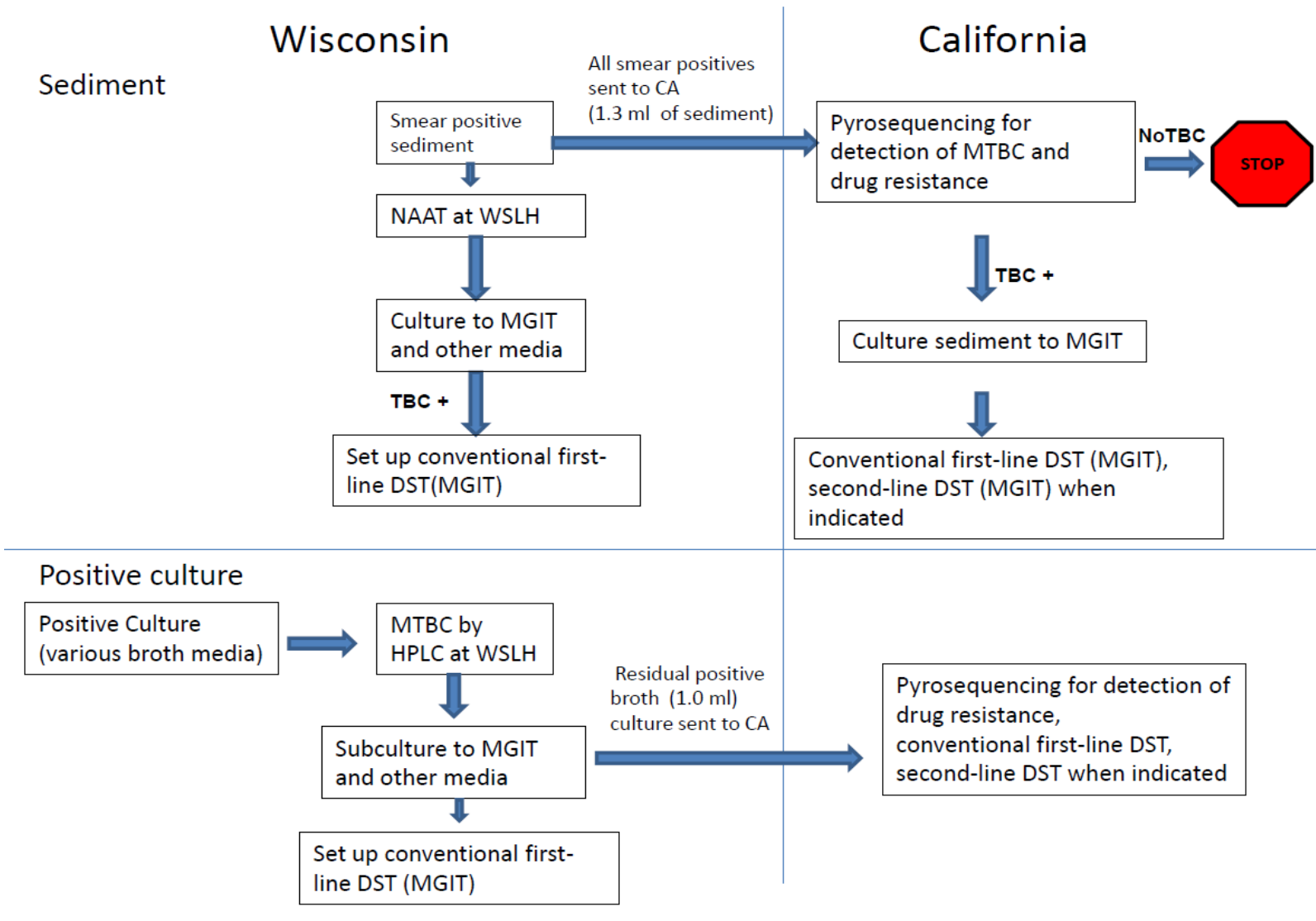
- Assess feasibility and consequences of referring smear-positive sediments to a reference laboratory for detection of TB by NAAT.
- Assess utility of universal referral of sediments and cultures for rapid molecular detection of drug resistance for a population at low risk for drug resistance.
- Assess feasibility and consequences of referring MTBC-positive sediments and cultures to a reference laboratory for conventional first- and second-line DST.

Shared Services Project

- Wisconsin State Laboratory of Hygiene (WSLH) referred specimens to the California Department of Public Health Laboratory (CDPHL)
 - Nucleic Acid Amplification Testing (NAAT)
 - Detection of drug resistance by molecular methods (PSQ=pyrosequencing)
 - Conventional TB first- and second-line drug susceptibility testing (DST)
- Wisconsin performed parallel NAAT and conventional TB first-line DST
- Nine-month study period (9/1/12 to 5/31/13)

Summary of California and Wisconsin Mycobacteriology Services

	CDPHL	WSLH
Nucleic Acid Amplification Testing (NAAT) for detection of <i>M. tuberculosis</i> complex	Pyrosequencing, <i>IS6110</i>	Laboratory-developed real-time PCR, <i>IS6110</i>
Detection of Drug Resistance by Molecular Methods	Pyrosequencing (PSQ) INH (<i>katG</i> , <i>inhA</i> , <i>ahpC</i>) rifampin (<i>rpoB</i>) fluoroquinolone (<i>gyrA</i>) injectables (<i>rrs</i>)	Referred to CDC for Molecular Detection of Drug Resistance (MDDR) program ⁴
TB first-line DST, Conventional	INH (two concentrations), rifampin, ethambutol, PZA by MGIT	INH (two concentrations), rifampin, ethambutol, PZA by MGIT
TB second-line DST, Conventional	Amikacin, moxifloxacin, ethionamide, and capreomycin by MGIT	Referred to CDC for agar proportion testing



Number of Specimens Referred to CDPHL and Number of Results Reported by CDPHL

Total number of specimens shipped	182
Number of patients with specimens shipped	162
Total number of shipments	90
NAAT: detection of <i>M. tuberculosis</i> complex from primary patient sediment	139
Detection of drug resistance (molecular)	47
Conventional TB First-line DST	41
Conventional TB Second-Line DST	13

Results

Submission and Transport Time

Time to Submission (average number of days from receipt at WSLH until send-out to CDPHL for Testing), smear + sediment	0.877 Range = 0-5 days
Average number of days in transit (FedEx or UPS)	1.13 Range = 1-5 days
TOTAL	2.0 days

Shipping Costs

Description	Unit Cost	Number of Packages	Total (\$)
Category A Shipment	Infectious shipper \$15.10 FedEx* overnight \$64.12	30	2,377
Category B Shipment	Shipper + cold pack \$15 UPS** overnight \$19.70	60	2,082
	TOTAL		\$4459

(*) Federal Express

(**) United Parcel Service

Shipping Summary

- Both FedEx and UPS offered rapid and reliable package transport (average 1.13 days for overnight service).
- Shipping costs were substantial (\$4459)
- Estimated labor costs for packaging and shipping would be $\$50 \times 90 = \4500

Detection of TB: Comparison of In-house and Referral Testing

NAAT for detection of <i>M. tuberculosis</i> complex (IS6110) from primary patient sediment	WSLH (real-time PCR)	Referral to CDPHL for detection of TB by PSQ
NAAT Results Reported	135	139
Number of culture-confirmed TB patients with positive NAAT from primary sediment	23/29 (79.3%)	27/29 (93.1%)
Average TAT from date of receipt in Wisconsin Lab (days)	0.31 Range = 0-4 days	3.84 Range = 1-11 days
Percent of Results meeting Healthy People 2020 Goal (identification of TB within 48 hours of receipt in WI Lab)	22/29 = 75.8%	7/29 = 24%

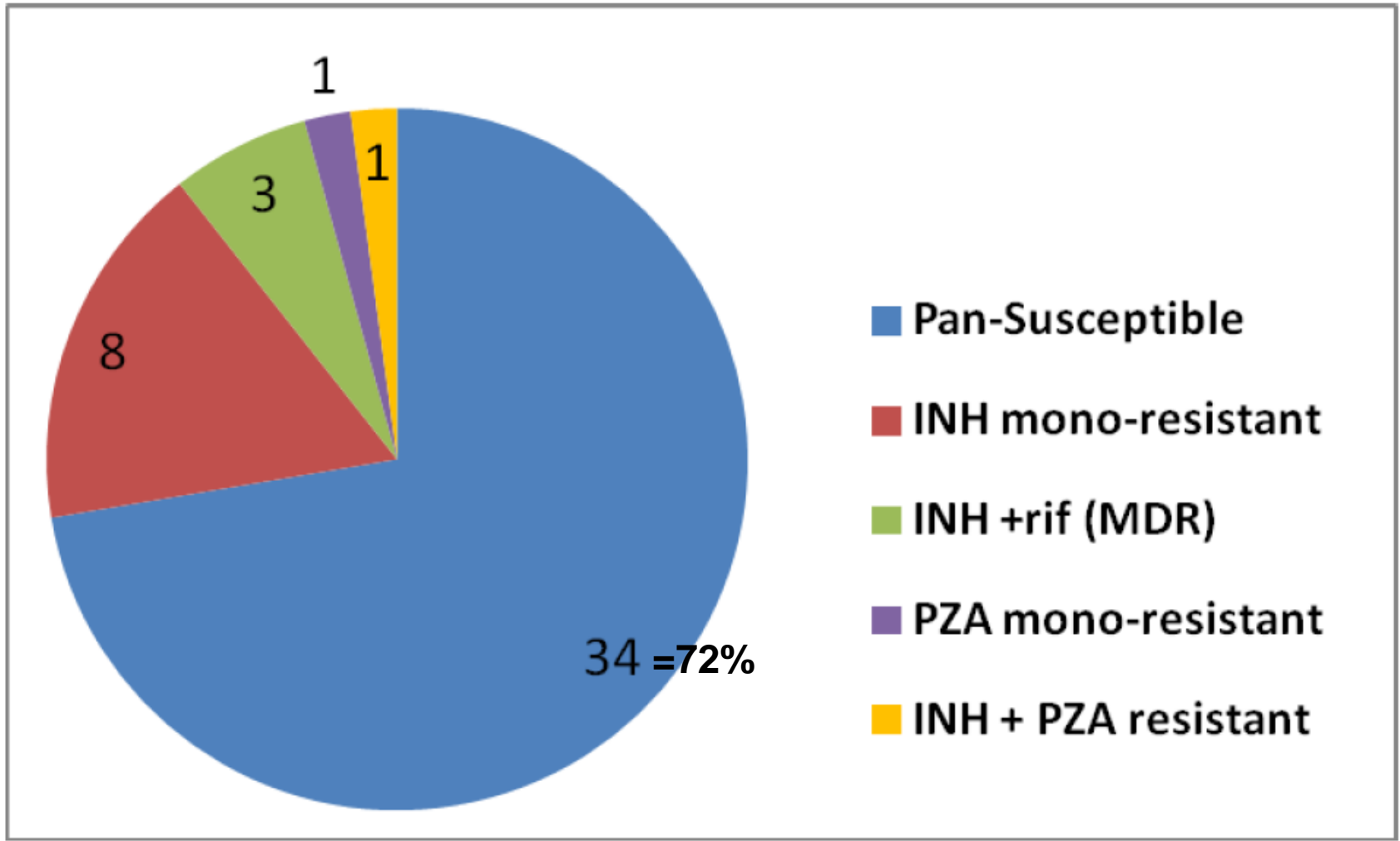
Summary: Referral for Detection of TB

- Although average time to submission for sediments (0.877 days) and average number of days in transit (1.13 days) were short, these delays had a substantial impact on NAAT TAT, despite excellent TAT (1.83 days) for NAAT at CDPHL.
- Only 24% of referred NAATs met the Healthy People 2020 Goal of detection of MTBC within 48 hours of specimen receipt.
- NAAT may not be as conducive to referral as other mycobacteriology testing due to the very short TATs required.

Detection of Drug Resistance

	WSLH	Referral to CDPHL
Average PSQ TAT from date of receipt in Wisconsin Lab (days)	Not performed	3.84 Range = 1-11
Median TAT: Conventional TB First Line DST, from date of receipt in Wisconsin Lab (days)	26 Range = 14-59	42 Range = 21-114
Median TAT: Conventional TB Second-Line DST, from date of receipt in Wisconsin Lab (days)	Not performed	41.5 Range = 27-115

Drug Resistance Detected



Summary: Detection of Drug Resistance by PSQ

- On average, PSQ results were reported 22 days before in-house conventional TB first-line DST results were complete.
- During the study, three new MDR-TB cases were rapidly identified using molecular testing.
- Based on PSQ results, conventional second-line DST could proactively be set up.
- PSQ results were routinely used by the Wisconsin TB Program to ensure appropriate therapy and patient management.

Use of PSQ results by WI TB Program

- **MDR-TB prediction:**
 - Full panel MDDR testing (including *embB* and *pncA* loci) is necessary for therapy decisions of new MDR-TB patients.
 - Continue any “susceptible” 1st line drugs, add fluoroquinolone and injectable
- **INH resistance prediction:**
 - Continue “susceptible” 1st line drugs, lengthen therapy, add moxifloxacin (?)

Use of PSQ results by WI TB Program

- **Pan-susceptible prediction:**
 - Gives TB program first prediction that the patient can be treated with 1st-line drugs
 - Assures nurses to continue standard therapy, even when the patient isn't doing well in the beginning
 - Good QA check for when conventional results are available (not necessary to repeat testing for “resistant” conventional result?)

Referral for Conventional DST

- Referral lead to a 16-day (median) delay in reporting conventional first-line DST results; TAT for referral for conventional TB first-line DST was 42 days.
- The CDPHL laboratory-developed MGIT assay for amikacin, moxifloxacin, ethionamide and capreomycin yielded rapid second-line DST results.
 - Additional drug testing (e.g. PAS, cycloserine, rifabutin) may be required for therapy decisions in some jurisdictions.

Discordant Results

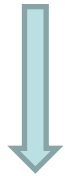
Nature of Discordance	Number of Events
NAAT: false negative in submitting lab, reference lab, or both	7
PSQ results don't agree with conventional results TB first-line DST	3
Conventional TB first line DST results don't agree between submitting lab and reference lab	3

Costs


Description	Unit Cost	Number Performed	Total (\$)
NAAT/PSQ	\$187	139	25,993
TB First-Line DST by MGIT	\$190	41	7,790
TB Second-line DST by MGIT	\$200	13	2,600
Packaging and Shipping	See slide 13		8,959
	TOTAL		\$45,342

Submitting Laboratory

Smear and Culture



NAAT or GeneXpert

MTBC positive sediment

MTBC-positive broth

Reference Laboratory

MDDR or PSQ



Conventional DST


Conclusions

- Through the CDC/APHL-funded Shared Services Project, we documented successes and challenges associated with sending specimens to a reference laboratory for mycobacteriology testing.
- Rapid TATs are imperative for NAAT. Achieving the Healthy People 2020 Goal of a 48-hour TAT was not possible in this Shared Services project.
- Sharing services provided rapid detection of drug resistance by PSQ to Wisconsin patients. These results were valuable for timely patient management decisions.

Conclusions (continued)

- Referral led to significant delays in conventional DST; these delays were not as consequential if molecular results were available.
- Laboratories should carefully consider testing options and consult with TB Control partners when making referral testing decisions.
- At a time when mycobacteriology laboratories may be experiencing staffing shortages and funding difficulties, reference laboratories can offer testing that may not otherwise be available. Benefits of referral testing may outweigh associated costs and delays.

Please see poster #6 for more details!



Exploring Novel Approaches to Shared TB Laboratory Services: California-Wisconsin Shared Services Pilot Study

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REVISED ABSTRACT

The pilot project shared microbiology laboratory services between public health laboratories, increasing both accuracy and efficiency. We designed a pilot to share a two TB reference state public health laboratory sediment culture methods and culture positive for all laboratories except in a high-volume public health laboratory for molecular and conventional microbiology testing. We related rate testing methods, where transmission, read report rates, test results, and test turnaround times.

Analysis of study data allowed us to assess the feasibility of sending specimens to a reference laboratory for TB diagnosis and conventional drug susceptibility testing. We also assessed the ability of reference lab to address and address for rapid molecular detection of drug resistance. This pilot study analyzed use in weekly high volume and existing local molecular and conventional microbiology laboratory services and determine the feasibility of shared services to reduce costs, improve efficiency and reduce errors.

INTRODUCTION and METHODS

Although laboratory (TL) services a significant burden to public and private health care organizations, reducing the number of TL tests continues to increase. For laboratories to avoid an increase in TL tests, it may be a struggle to offer a full spectrum of TL laboratory services in the face of ever-increasing test volume. Despite regulatory barriers and retention of essential laboratory professionals contribute to this struggle. To maintain quality laboratory testing and to reduce expenses, laboratories may consider a shared service option. A low-volume laboratory could submit specimens to a large reference laboratory for specialized testing if a group of smaller laboratories could serve specific cities or regions, each providing a portion of the necessary testing. Laboratories are looking to explore these opportunities as many aspects of shared laboratory services have not been fully explored.

For the nine-month study period (2015-2016) the Wisconsin State Laboratory of Hygiene (WSLH) referred an aliquot of each smear positive sediment to the California Department of Public Health Laboratory (CDPH) for detection of TB (conventional culture (CC) and detection of isoniazid and rifampin drug resistance. CDPH used their MTBC-positive sediments to refer to their culture for conventional first-line drug susceptibility testing (DST) and performed second-line testing for isoniazid and rifampin on any but the first drug. Molecular confirmed culture (mcc) and rapid molecular testing (RMT) and conventional TB first-line DST (see Table 1 and Figure 1).

	CDPH	WSLH
MAAT	Preprocessing, RMT	Preprocessing, RMT, Line CXR, DST
Detection of Drug Resistance by Molecular Methods	ISN, IAS, and RIF	ISN, IAS, and RIF
First-line DST	Conventional	ISN, IAS, and RIF
Second-line DST	Conventional	ISN, IAS, and RIF

Table 2. Number of Specimens Referred to CDPH, and Number of Results Reported by CDPH.

	2015
Total number of specimens referred	762
Number of patients with specimens referred	762
Total number of results reported	108
CDPH submission of RMT from clinical specimens	108
Detection of Drug Resistance (Conventional)	47
Conventional TB First-Line DST	47
Conventional TB Second-Line DST	12

REFERENCES

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2. Wisconsin State Laboratory of Hygiene. <http://www.wisconsin.gov/hygiene>

3. California Department of Public Health. <http://www.cdph.ca.gov>

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Figure 1. Flow of Testing during California-Wisconsin Shared Services Pilot Study




Figure 2. Detection of Drug Resistance by P52 (n=47)



SUMMARY

- Both Federal Express and United Parcel Service (UPS) offered rapid and reliable package shipment (average 1-33 days for overnight shipping, average shipping costs were minimal). Total shipping cost for 32 category A and 63 category B packages was \$2455. This cost includes shipping materials but does not include labor for packaging.
- Although average time to submission for sediments (3.07 days) and average number of days to result (1.13 days) were short, these delays had a substantial impact on MAAT TB (Table 4). Only 24% of referred MAATs met the Healthy People 2020 goal of median of 48 hours of specimen receipt, despite excellent TB (1.81 days) for MAAT at CDPH.
- Preprocessing (RMT)
 - On average, RMT results were reported 22 days before isoniazid conventional TB first-line DST results (Table 5).
 - During the study three new RMT TB cases were rapidly identified using molecular testing (Figure 3).
 - Full-panel molecular testing (including smear and gene loci) was necessary for therapy decisions for new RMT TB patients.
 - TB First-Line and Second-Line DST
 - Referal led to a 16-day (median) delay in reporting conventional first-line DST results.
 - The median DST for referred TB first-line DST was 42 days overall (Table 5). This DST (reported in 32 days when pure MAAT growth was used for testing instead of some positive quality sediments to testing occurred) if sediments were contaminated with non-TB organisms or clinical contain viable organisms.
 - The CDPH laboratory developed RMT assay for molecular confirmation, isoniazid and rifampin (rapid) second-line DST results. Additional drug testing by RMT, isoniazid, rifampin may be required for therapy decisions in some jurisdictions.

CONCLUSIONS

- We encountered successes and challenges associated with sending specimens to a reference laboratory for microbiology testing through the WSLH/CDPH shared services project.
- Feasibility of sending specimens to a reference laboratory for MAAT Rapid TB cases for the MAAT. Testing the Healthy People 2020 goal of a 48-hour TB test was possible in the Shared Services project primarily due to submission and transport times.
- Utility of reference lab of sediments and cultures for rapid detection of drug resistance (ie RMT) for a population at low risk for drug resistance. RMT results were readily used by the Wisconsin TB Program and were especially useful for patients with the history for drug resistance. For jurisdictions that do not have RMT testing capabilities, having a reference laboratory available would be available for the management of TB patients.
- Feasibility of referring MTBC-positive sediments and cultures to a reference laboratory for conventional first and second-line DST. Referal led to significant delays in conventional DST. These delays were not an unexpected if molecular results were available.
- Future Directions: As a line when microbiology laboratories may be expanding staff shortages and testing efficiency, reference laboratories can be testing that may not otherwise be available. In some cases, volume of specimens may lead to delays in reporting test results. Laboratory should consider using testing options and consult with TB control partners when making referral/testing decisions.

RESULTS

Table 3. Submission and Transport Time

Time to Submission (average number of days from receipt at WSLH and sent out to CDPH, for weekly) for smear and/or sediment	0.817 Range = 0-5 days
Average number of days in transit (Federal Express or United Parcel Service)	1.13 days Range = 1-15.5 days
TOTAL	2.0 days

Table 4. Comparison of In-house and Referred MAAT

MAAT for detection of ISN, IAS, and RIF (MAAT Above)	RMT (MAAT Above)	Referal to CDPH for MAAT + P52
Number of culture confirmed TB patients with positive MAAT from specimens at WSLH	120	120
Number of culture confirmed TB patients with positive MAAT from specimens at WSLH	2028 (96.3%)	2720 (96.1%)
Average DST was rate of result to Molecular Laboratory	DST Range = 0-5.0 days	3.88 Range = 0-11.0 days
Percent of Results meeting Healthy People 2020 Goal ¹	CDPH = 75.8%	CDH = 28%

Table 5. TB¹ for Detection of Drug Resistance

Test	WSLH TB (days) DST (days)	Referal to CDPH TB (days) DST (days)
P52	Not performed	Average=40.88 Range = 0-15 days
Conventional TB First-Line DST (MAAT)	Median=26 Range= 24-90 days	Median = 42 Range = 2-1124 days
Conventional TB Second-Line DST (MAAT)	Not performed	Median = 42.3 Range = 27-118 days

(¹) From date of receipt at Wisconsin Laboratory

CDPHL Laboratory Team

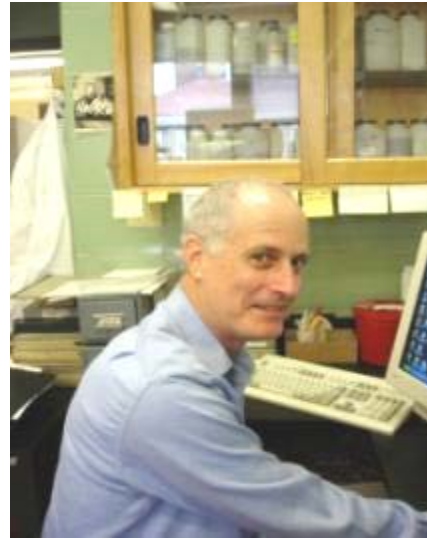


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